REMARKS

Claim 5 has been amended to correct the inadvertent failure to alter the claim dependency in the previous amendment. The amendment is for clarification and no new matter has been added. Entry of the amendment is thus requested.

The sole basis for rejection is for asserted obviousness over the combination of Little, II., *et al.*, U.S. patent 6,376,211 in view of Kim, *et al.*, or Hayakawa, *et al.* Little discloses that bactericidal/permeability-increasing protein which is an antibacterial compound isolated from neutrophils. BPI has a number of activities, including neutralizing the anti-coagulant activity of heparin and as an anti-thrombotic. According to column 6, beginning at line 66, the disclosure in Little is

> based on the discovery that a class of antimicrobial agents derived from bactericidal/permeability-increasing protein (BPI) acts by a unique mechanism involving inhibition of ATP-synthase (F_1/F_0 ATPase). Members of the F_1/F_0 family of ATP synthases are present in bacteria, in chloroplast membranes and in mitochondria.

Thus, the teaching of Little, II is simply that BPI, which is known to be an antibacterial, exerts its antibacterial effects through this mechanism. The Office appears to conclude, therefore, that it must follow that the apoptotic effects of apoptolidin are also exerted through thus mechanism. But it does not follow. There are many other mechanisms by which apoptolidin might exert this effect.

First, effecting apoptosis is not the same as inhibiting proliferation. Applicants apologize that this point was not more forcefully made in their previous response. The fact that inhibition of ATP synthase will result in lack of proliferation does not mean that such inhibition will result in apoptosis which requires the actual death of the cells in question.

Thus, any correlation between ATP synthase inhibition and anti-proliferation does not lead to a conclusion that there is a correlation between inhibition of ATP synthase and apoptosis.

However, even if that were true, it would not follow that assessing analogs of apoptolidin for ATP synthase activity would be a productive way to identify additional compounds that are able to induce apoptosis. This is because there is nothing in Little or any other cited document which shows that the manner in which apoptolidin exerts this effect is through inhibition of ATP synthase. If it is not, then there is no point in assessing apoptolidin relatives for this ability; they may very well be apoptotic without inhibiting ATP synthase. If it is not the mechanism by which apoptosis is induced, one would predict that negative results would be obtained even though the compounds might themselves induce apoptosis.

Thus, there is no motivation to combine Little with Kim or Hayakawa which merely disclose that apoptolidin has apoptotic properties. The combination would only be motivated if it were predictable that the mechanism by which apoptolidin has its observed effects is through inhibition of this synthase. But that is not established in the art; it is established only by the present inventors.

Accordingly, there is no motivation to combine Little with Kim or Hayakawa and once combined, the invention does not result since neither Kim nor Hayakawa suggests any derivatives of apoptolidin other than a single truncated form, or that they be tested for anything other than apoptotic effect per se and there is nothing in the art which would lead one to believe that this family of compounds exerts its apoptotic effects through ATP synthase inhibition.

Based on the foregoing, it is respectfully requested that the rejection be withdrawn.

The inclusion of claim 5 in this rejection appears also to be an error. There is nothing in the art cited by the Office that suggests preparing an analog of apoptolidin from a modified form of the synthase for apoptolidin or of its tailoring enzymes. No document has been cited which

makes this suggestion. Accordingly, clearly claim 5 is free of the cited art and should be passed to allowance.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 286002021220.

Respectfully submitted,

Dated: September 8, 2003 By: Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125